# Varenicline tartrate (CHAMPIX®) Application for Inclusion in the WHO Essential Medicines List November 2020

Submitted by Pfizer Inc

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## GENERAL ITEMS

### 1. Summary statement of the proposal for inclusion, change or deletion.

This application is designed to support the inclusion of varenicline as a smoking cessation treatment in the World Health Organization (WHO) Essential Medicines List.

The significant worldwide burden of illness imposed by smoking, and the reduction in that burden achieved by quitting, are both well-documented, placing smoking cessation among the most valuable of public health intervention.[1,2] The WHO describes tobacco use as one of the leading preventable cause of death and illness in the world. Smoking increases the risk of developing cardiovascular disease, respiratory illnesses such as chronic obstructive pulmonary disease (COPD), and several types of cancer.[1] In addition, early evidence suggests that smokers who are hospitalized with SARS-CoV-2 infection are at higher risk for severe disease and death compared to non-smokers.[3] Worldwide, approximately 1.0 billion people smoke cigarettes and approximately 8 million people continue to die every year from smoking related disease.[2,4]

The most recent WHO report on global trends in tobacco showed that between 2000-2015 there was a net decrease of 28.6 million smokers worldwide. The largest reductions in smoking were found in the Americas and Europe, followed by smaller decreases in South-East Asia. In contrast, the number of smokers in African, Eastern Mediterranean, and Western Pacific regions has increased during that same time period. In general, high-income countries saw a greater decline in smoking than those in lower-middle or low-income countries which reported increases in the number of smokers between 2000-2015. Middle and low-income countries reporting the highest daily incidence of smoking include: China (267 million [M]), India (92M), Indonesia (63M), Brazil (18M), and Mexico (7M). Thus, although global tobacco control measures have resulted in a net decrease in the incidence and prevalence of smoking worldwide, the impact of tobacco control has not been consistent across all regions and income groups.[2]

Offering help to quit tobacco use was identified by the WHO Framework Convention on Tobacco Control as one of the major tobacco control measures to further counter the tobacco epidemic.[5] The health benefits of quitting smoking and its impact on smoking-related diseases have been firmly established[6,7,8]. Despite this, smoking prevalence in individuals aged 15 and older in the EU was 22.5% in 2014[9] and an estimated 13.9% of adults in the United States (US) still smoke.[10] The numbers of smokers in some developing countries are even more concerning. As many as 70% of smokers say they want to quit.[11] However, for many smokers, smoking is not a lifestyle choice or habit, but an addiction to nicotine. Less than 5% of smokers are able to quit on their own and remain abstinent up to 1 year.[12] Smoking cessation interventions, including counselling and medication, can more than double the chance that a smoker who tries to quit will succeed.[13] Article 14 of the WHO Framework Convention on Tobacco Control calls for evidence-based medications for smoking cessation to be made available for smokers who want to quit. Other than varenicline, only two approved pharmacotherapies for smoking cessation are widely

used globally: nicotine replacement therapies and bupropion. In a 2016 survey of 61 countries with smoking cessation treatment guidelines, overall, 98% recommended nicotine replacement therapy (NRT), 84% bupropion, and 82% varenicline. Interestingly, the percentage recommending varenicline did not differ significantly from high-income to upper-middle-income to lower-middle-income countries, no low-income countries reported having guidelines.[14]

Varenicline is indicated as an aid to smoking cessation in adults 18 years and older.[15,16] The efficacy of varenicline in smoking cessation is believed to be the result of varenicline activity at the α4β2 sub-type of the nicotinic receptor family. Varenicline binding to α4β2 neuronal nicotinic acetylcholine receptors stimulates receptor mediated activity, but at a significantly lower level than nicotine. Varenicline also blocks the ability of nicotine to activate α4β2 receptors and thus to stimulate the central nervous mesolimbic dopamine system, believed to be the neuronal mechanism underlying reinforcement and reward experienced upon smoking.[17]

Varenicline has received regulatory approval in 116 countries. The cumulative worldwide exposure to varenicline is estimated to be 6,732,728 patient-years.

Cumulatively, it is estimated that 24,654 subjects have participated in Pfizer-initiated varenicline clinical trials worldwide. The 47 countries participating in these trials span North America (Canada, United States), Central and South America (Argentina, Chile, Colombia, Costa Rica Brazil, Mexico, Venezuela), Western Europe (Belgium, Denmark, Finland, France, Germany, Greece, Italy, Netherlands, Norway, Sweden, Spain, Switzerland, United Kingdom), Eastern Europe (Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Hungary, Romania, Slovakia), the Republic of Georgia, the Russian Federation, the Middle East (Egypt, Lebanon, Jordan, Qatar, Saudi Arabia, United Arab Emirates), Africa (South Africa), Asia (China, Japan, Republic of Korea, Singapore, Taiwan, Thailand) and Oceania (Australia, New Zealand). Additionally, it is estimated that 4,837 patients from Pfizer-sponsored non-interventional studies have been exposed to varenicline worldwide since the product was first approved. The results of the pivotal studies and those in key populations are presented in this report. In addition, the safety data for varenicline from these clinical trials are reviewed, and the cost-effectiveness data based on clinical trial results are presented.

In the largest pharmacotherapy smoking cessation trial of its kind conducted to date (over 8,000 participants), a double-blinded head-to-head study (Evaluating Adverse Events in a Global Smoking Cessation Study [EAGLES] Study A3051123) of three approved smoking cessation medications compared to placebo and each other, showed that varenicline was more effective than bupropion or nicotine patch in helping smokers with and without a history of psychiatric disorder achieve abstinence, while all 3 treatments showed benefit over placebo.[18] In a 2016 *Cochrane Database of Systematic Reviews*, which included the EAGLES study, the authors found that the number needed to treat to achieve an additional beneficial outcome (NNTB) was 11 (95% confidence interval [CI] 9 to 13) for varenicline, while the NNTB for all types of NRT was 23 (95% CI 20 to 25), and the NNTB for

bupropion was 22 (95% CI 18 to 28). These calculations assumed a control quit rate with behavioral support at six months of 7.5%.[19]

The EAGLES study also demonstrated the neuropsychiatric safety of varenicline, as well as of bupropion and NRT, compared to placebo. The concern about the neuropsychiatric safety of patients treated with varenicline was initially driven by case reports from post-marketing surveillance that included events such as suicidal ideation and behavior and completed suicide, changes in mood, psychosis, aggression, and hostility. The EAGLES study was a US post-marketing requirement and a European Union (EU) post-authorization safety study designed to assess the neuropsychiatric safety profile of varenicline and bupropion as aids to smoking cessation in smokers with and without a history of psychiatric disorder.

Overall, smoking cessation therapy is believed to be a cost-effective intervention.[2] In evaluations using the Benefits of Smoking Cessation on Outcomes (BENESCO) model, 12 weeks of therapy with varenicline was predicted to be more effective and less costly from the healthcare payer perspective over a 20 year or lifetime horizon, relative to bupropion, NRT, or unaided quitting. These results are relatively consistent across countries with different levels of economic development; however, most of the assessments have taken place in high and middle-income countries.[20,21,22] Health technology assessment (HTA) bodies in several markets have concluded that treatment with varenicline has an acceptable cost-benefit profile as evidenced by its reimbursement status in countries across several regions including North America, Europe, Africa, the Middle East and Asia Pacific.

Smokers who would like to quit should have a variety of options. Varenicline has been demonstrated to be an effective aid to smoking cessation that is superior to single NRT approaches both in the large head-to-head study and in the Cochrane meta-analyses and another detailed systematic review.[23] As such, varenicline warrants inclusion in the WHO Essential Medicines List.

**2. Name of the WHO technical department and focal point supporting the application (where relevant).**

WHO Tobacco Free Initiative (TFI), focal point being Dr. Vinayak Mohan Prasad
email:_prasadvi@who.int

**3. Name of organization(s) consulted and/or supporting the application.**

Campaign for Tobacco-Free Kids
1400 I Street NW, Suite 1200
Washington, DC 20005
www.tobaccofreekids.org/

World Heart Federation
32, rue de Malatrex,
1201 Geneva, Switzerland
www.world-heart-federation.org

## 4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

Varenicline
Varenicline tartrate
ATC Code: N07BA03

## 5. Formulation(s) and strength(s) proposed for inclusion; including adult and pediatric (if appropriate).

Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX 0.5 mg
Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX 1 mg

## 6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.

This application is for the inclusion of varenicline tartrate as an individual medicine to the WHO Essential Medicines List.

## TREATMENT DETAILS, PUBLIC HEALTH RELEVANCE AND EVIDENCE APPRAISAL AND SYNTHESIS

## 7. Treatment details (requirements for diagnosis, treatment and monitoring).

### Usual Dosage for Adults[15]

Smoking cessation therapies are more likely to succeed for patients who are motivated to stop smoking and who are provided additional advice and support. Patients should be provided with appropriate educational materials and counseling to support the quit attempt.

The patient should set a date to stop smoking. Varenicline dosing should begin one week before this date. Alternatively, the patient can begin varenicline dosing and then quit smoking between days 8 and 35 of treatment.

Varenicline should be taken orally after eating and with a full glass of water.

The recommended dose of varenicline is 1 mg twice daily following a 1-week titration as follows:

| | |
|---|---|
| Days 1 – 3: | 0.5 mg once daily |
| Days 4 – 7: | 0.5 mg twice daily |
| Day 8 – end of treatment: | 1 mg twice daily |

Patients should be treated with varenicline for 12 weeks. For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment with varenicline is recommended to further increase the likelihood of long-term abstinence.

For patients who are sure that they are not able or willing to quit abruptly, a gradual approach to quitting smoking with varenicline may be considered. Patients should begin varenicline dosing and reduce smoking by 50% from baseline within the first four weeks, by an additional 50% in the next four weeks, and continue reducing with the goal of reaching complete abstinence by 12 weeks. Varenicline treatment should then be continued for an additional 12 weeks, for a total of 24 weeks of treatment. Patients should be encouraged to attempt quitting sooner if they feel ready.

Patients who are motivated to quit, and who did not succeed in stopping smoking during prior varenicline therapy for reasons other than intolerability due to adverse events (AEs) or who relapsed after treatment, should be encouraged to make another attempt with varenicline once factors contributing to the failed attempt have been identified and addressed.

A temporary or permanent dose reduction should be considered for patients who cannot tolerate the adverse effects of varenicline.

**Dosage in Special Populations**

Patients with Impaired Renal Function

No dosage adjustment is necessary for patients with mild to moderate renal impairment. For patients with severe renal impairment (estimated creatinine clearance less than 30 mL per min), the recommended starting dose of varenicline is 0.5 mg once daily. The dose may then be titrated as needed to a maximum dose of 0.5 mg twice daily. For patients with end-stage renal disease undergoing hemodialysis, a maximum dose of 0.5 mg once daily may be administered if tolerated.

Elderly and Patients with Impaired Hepatic Function

No dosage adjustment is necessary for patients with hepatic impairment. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

**Pregnancy**

Regarding the use of varenicline in pregnancy, the product labeling differs by region. The EMA notes there is a moderate amount of data on pregnant women that indicate no malformative or fetal/neonatal toxicity of varenicline. However, animal studies have shown reproductive toxicity, and as a precautionary measure, EMA notes it is preferable to avoid the use of varenicline during pregnancy. The US labeling does not contain a specific recommendation. Thus, health care providers should consult the local summary of product characteristics (SmPC) regarding the

use of varenicline in pregnancy. Below is a summary of the available data on varenicline in pregnant and lactating women.[15,16]

Risk Summary

Available data have not suggested an increased risk for major birth defects following exposure to varenicline in pregnancy, compared with women who smoke (see Human Data). Smoking during pregnancy is associated with maternal, fetal, and neonatal risks (see Clinical Considerations). In animal studies, varenicline did not result in major malformations but caused decreased fetal weights in rabbits when dosed during organogenesis at exposures equivalent to 50 times the exposure at the maximum recommended human dose (MRHD). Additionally, administration of varenicline to pregnant rats during organogenesis through lactation produced developmental toxicity in offspring at maternal exposures equivalent to 36 times human exposure at the MRHD (see Animal Data).

The estimated background risk of oral clefts is increased by approximately 30% in infants of women who smoke during pregnancy, compared to pregnant women who do not smoke. The background risk of other major birth defects and miscarriage for the indicated population are unknown. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Clinical Considerations

*Disease-Associated Maternal and/or Embryo/Fetal Risk*

Smoking during pregnancy causes increased risks of orofacial clefts, premature rupture of membranes, placenta previa, placental abruption, ectopic pregnancy, fetal growth restriction and low birth weight, stillbirth, preterm delivery and shortened gestation, neonatal death, sudden infant death syndrome and reduction of lung function in infants. It is not known whether quitting smoking with varenicline during pregnancy reduces these risks.

Data

*Human Data*

A population-based observational cohort study using the national registers of Denmark and Sweden compared pregnancy and birth outcomes among women exposed to varenicline (N=335, includes 317 first trimester exposed) with women who smoked during pregnancy (N=78,412) and with non-smoking pregnant women (N=806,438). The prevalence of major malformations, the primary outcome, was similar in all groups, including between smoking and non-smoking groups. The prevalence of adverse perinatal outcomes in the varenicline-exposed cohort was not greater than in the cohort of women who smoked and differed somewhat between the three cohorts.[24] The prevalences of the primary and secondary outcomes are shown in Table 1.

**Table 1. Summary of Primary and Secondary Outcomes for Three Birth Cohorts**

| Outcome | Varenicline Cohort (n=335) | Smoking Cohort (n=78,412) | Non-Smoking Cohort (n=806,438) |
|---|---|---|---|
| Major congenital malformation[a] | 12 / 334 (3.6%) | 3,382 / 78,028 (4.3%) | 33,950 /804,020 (4.2%) |
| Stillbirth | 1 (0.3%) | 384 (0.5%) | 2,418 (0.3%) |
| Small for gestational age | 42 (12.5%) | 13,433 (17.1%) | 73,135 (9.1%) |
| Preterm birth | 25 (7.5%) | 6,173 (7.9%) | 46,732 (5.8%) |
| Premature rupture of membranes | 12 (3.6%) | 4,246 (5.4%) | 30,641 (3.8%) |
| Sudden infant death syndrome[b] | 0/307 (0.0%) | 51/71,720 (0.1%) | 58/755,939 (<0.1%) |

a. Included only live births in the cohorts. Prevalence among first trimester varenicline-exposed pregnancies (11/317 [3.5%]).
b. There was a lag in death data in Denmark, so the cohorts were smaller.

The study limitations include the inability to capture malformations in pregnancies that do not result in a live birth, and possible misclassification of outcome and of exposure to varenicline or to smoking.

Other small epidemiological studies of pregnant women exposed to varenicline did not identify an association with major malformations, consistent with the Danish and Swedish observational cohort study. Methodological limitations of these studies include small samples and lack of adequate controls.

Overall, available studies cannot definitely establish or exclude any varenicline-associated risk during pregnancy.

*Animal Data*

Pregnant rats and rabbits received varenicline succinate during organogenesis at oral doses up to 15 and 30 mg/kg/day, respectively. While no fetal structural abnormalities occurred in either species, maternal toxicity, characterized by reduced body weight gain, and reduced fetal weights occurred in rabbits at the highest dose (exposures 50 times the human exposure at the MRHD of 1 mg twice daily based on AUC). Fetal weight reduction did not occur in rabbits at exposures 23 times the human exposure at the MRHD based on AUC.

In a pre- and postnatal development study, pregnant rats received up to 15 mg/kg/day of oral varenicline succinate from organogenesis through lactation. Maternal toxicity, characterized by a decrease in body weight gain, was observed at 15 mg/kg/day (36 times the human exposure at the MRHD based on AUC). However, decreased fertility and increased auditory startle response occurred in offspring at the highest maternal dose of 15 mg/kg/day.

**Lactation**

Risk Summary

There are no data on the presence of varenicline in human milk, the effects on the breastfed infant, or the effects on milk production. In animal studies, varenicline was present in milk of lactating rats (see Data). However, due to species-specific differences in lactation physiology, animal data may not reliably predict drug levels in human milk. The lack of clinical data during lactation precludes a clear determination of the risk of varenicline to an infant during lactation; however, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for varenicline and any potential adverse effects on the breastfed child from varenicline or from the underlying maternal condition.

Clinical Considerations

Because there are no data on the presence of varenicline in human milk and the effects on the breastfed infant, breastfeeding women should monitor their infant for seizures and excessive vomiting, which are adverse reactions that have occurred in adults that may be clinically relevant in breastfeeding infants.

Data

In a pre- and postnatal development study, pregnant rats received up to 15 mg/kg/day of oral varenicline succinate through gestation and lactation. Mean serum concentrations of varenicline in the nursing pups were 5–22% of maternal serum concentrations.

**Pediatric Use**

Varenicline is not recommended for use in pediatric patients 16 years of age or younger because its efficacy in this population was not demonstrated.

Single and multiple-dose pharmacokinetics of varenicline have been investigated in pediatric patients aged 12 to 17 years old (inclusive) and were approximately dose-proportional over the 0.5 mg to 2 mg daily dose range studied. Steady-state systemic exposure in adolescent patients of bodyweight >55 kg, as assessed by AUC (0-24), was comparable to that noted for the same doses in the adult population. When 0.5 mg BID was given, steady-state daily exposure of varenicline was, on average, higher (by approximately 40%) in adolescent patients with bodyweight ≤55 kg compared to that noted in the adult population.

The efficacy and safety of varenicline were evaluated in a randomized, double-blind, placebo-controlled study of 312 patients aged 12 to 19 years, who smoked an average of at least 5 cigarettes per day during the 30 days prior to recruitment, had a score of at least 4 on the Fagerström Test for Nicotine Dependence scale, and at least one previous failed quit attempt. Patients were stratified by age (12 to 16 years of age, n=216 and 17 to 19 years of age, n=96) and by body weight (≤55 kg and >55 kg). Patients were randomized to one of two doses of varenicline, adjusted by weight to provide plasma levels in the efficacious range (based on adult studies)

and placebo. Patients received treatment for 12 weeks, followed by a non-treatment period of 40 weeks, along with age-appropriate counseling throughout the study. Results from this study showed that varenicline, at either dose studied, did not improve continuous abstinence rates at weeks 9 through 12 of treatment compared with placebo in subjects 12 to 19 years of age. The varenicline safety profile in this study was consistent with that observed in adult studies.

**Geriatric Use**

A combined single- and multiple-dose pharmacokinetic study demonstrated that the pharmacokinetics of 1 mg varenicline given once daily or twice daily to 16 healthy elderly male and female smokers (aged 65–75 years) for 7 consecutive days was similar to that of younger subjects. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Varenicline is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

No dosage adjustment is recommended for elderly patients.

**8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)**

Smoking remains among the leading causes of preventable death and disease worldwide and is a major global public health challenge.[1,2] The WHO estimates there are more than 1.3 billion tobacco users and approximately 80% of them live in low- and middle-income countries. While the prevalence of smoking has been declining across all income groups and in almost every region throughout the world (except Africa and the Middle East which appear to be flat), the average global smoking rate remains unacceptably high (19.2%) and approximately 8 million people continue to die every year from smoking related diseases.[2,4]

Furthermore, the global economic burden associated with smoking-attributable morbidity and mortality is substantial. One study estimated global healthcare cost for smoking-related diseases at approximately US $467 billion, which is roughly 5.7% of the total global healthcare expenditure. When accounting for loss of productivity, the total economic burden of smoking is estimated at more than US $1 trillion per year.[25]

The causal relationship between smoking tobacco and numerous disease processes, including cardiovascular disease (CVD), multiple types of cancer (eg, bladder and lung), and pulmonary disease (eg, COPD and emphysema), is well-established.[1] For example, it is estimated that adults who smoke 20 cigarettes per day increase their relative risk of an ischemic event by more than 50%, and of the 9.4 million deaths

attributed to CHD worldwide, approximately 18% of these cases are caused by smoking.[26,27,28] Additionally, smokers are at 15-30 times the risk of developing lung cancer compared to those who have never smoked, and are 4 times more likely to develop bladder cancer than non-smokers.[29,30] Smoking is also the leading cause of COPD and 73% of disease-related mortality in high-income countries is attributable to smoking.[31,32] Taken together, those who smoke may on average have a ten-year shorter life expectancy than people who have never smoked.[33]

Fortunately, there are benefits to quitting smoking at almost any age, and those who successfully quit may significantly reduce the risk of developing or dying from smoking-related diseases.[1,2] For example, ten years after quitting smoking, the risk of developing lung cancer is 50% lower compared to people who continue to smoke, and after 15 years of quitting, the risk of developing CVD is almost comparable to someone who has never smoked. There are also short-term benefits to health that occur only weeks or months following smoking cessation, such as reduced frequency of cough and shortness of breath, as well as improved circulation and lung function.[1,2]

The majority of smokers, approximately 60-68%, would like to quit smoking, and it is estimated that 40% of smokers report making a quit attempt within the last 12 months, although many of these attempts are unsuccessful.[1,2] In some low and middle-income countries with high smoking prevalence, such as China, India, Indonesia and Brazil, the number of adults who indicated they were thinking of quitting was slightly lower, approximately 40%, 45%, 50% and 50%, respectively.[2] The most common cessation approach taken by smokers is to make an unaided quit attempt, also known as quitting 'cold turkey'; it is estimated that about 4-8% of unaided quit attempts are successful.[1,2] Several well-established guidelines backed by high-quality evidence consider the combination of behavioral support and pharmacotherapy as the most effective way to quit smoking in the short and long term.[13,34], Although the efficacy of smoking cessation interventions varies, the combination of medication and behavioral support can as much as double a smoker's chances of quitting; the provision of medication or behavioral support alone have both been found superior to an unaided quit attempt.[2,13] The uptake of interventions is dependent on both availability (ie, access and cost) and on smoker's preferences, which are likely to differ across social and cultural contexts. Therefore, the ability to offer a range of smoking cessation options is critical to facilitate maximal uptake and optimal treatment effectiveness.[2]

## 9. Review of benefits: summary of comparative effectiveness in a variety of clinical settings.

### Important Baseline Efficacy and Effectiveness Information

Varenicline was first approved as an aid to smoking cessation treatment in adults in the United States (as CHANTIX ®) in May 2006, and in the EU as CHAMPIX® in September 2006.

Varenicline binds with high affinity and selectivity at the α4β2 neuronal nicotinic acetylcholine receptors, where it acts as a partial agonist: a compound that has

both agonist activity, with lower intrinsic efficacy than nicotine, and antagonist activities in the presence of nicotine. Electrophysiology studies in vitro and neurochemical studies in vivo have shown that varenicline binds to the α4β2 neuronal nicotinic acetylcholine receptors and stimulates receptor-mediated activity, but at a significantly lower level than nicotine. Varenicline competes for the same human α4β2 nAChR (nicotinic acetylcholine receptor) binding site for which nicotine has lower affinity. Therefore, varenicline can effectively block nicotine's ability to fully activate α4β2 receptors and the mesolimbic dopamine system, the neuronal mechanism underlying reinforcement and reward experienced upon smoking. The efficacy of varenicline in smoking cessation is a result of varenicline's partial agonist activity at the α4β2 nicotinic receptor where its binding produces an effect sufficient to alleviate symptoms of craving and withdrawal (agonist activity), while simultaneously resulting in a reduction of the rewarding and reinforcing effects of smoking by preventing nicotine binding to α4β2 receptors (antagonist activity).[17]

## Clinical Efficacy

Two identically designed double-blind pre-authorization clinical trials (A3051028[35] and A3051036[36]) prospectively compared the efficacy of varenicline (1 mg twice daily), sustained release bupropion (150 mg twice daily), and placebo in smoking cessation. In these 52-week duration studies, patients received treatment for 12 weeks, followed by a 40-week non-treatment phase. Patients were provided with an educational booklet on smoking cessation and received up to 10 minutes of smoking cessation counselling at each weekly treatment visit according to Agency for Healthcare Research and Quality guidelines. Patients set a date to stop smoking (target quit date) with dosing starting 1 week before this date.

The primary endpoint of the two studies was the carbon monoxide (CO) confirmed, 4-week continuous abstinence (CA) rate from week 9 through week 12. The primary endpoint for varenicline demonstrated statistical superiority to bupropion and placebo. After the 40-week non-treatment phase, a key secondary endpoint for both studies was the CA at week 52. CA was defined as the proportion of all subjects treated who did not smoke (not even a puff of a cigarette) from Week 9 through Week 52 and did not have an exhaled CO measurement of > 10 ppm. The CA rates during weeks 9-12 and 9-52 from these studies are included in Table 2.

**Table 2. Continuous Abstinence during Weeks 9-12 and 9-52 in Preauthorization Studies**

| | Study A3051028 (n=1022) | | Study A3051036 (n=1023) | |
|---|---|---|---|---|
| | **CA Wk 9-12** | **CA Wk 9-52** | **CA Wk 9-12** | **CA Wk 9-52** |
| **Varenicline** | 44.4% | 22.1% | 44.0% | 23.0% |
| **Bupropion** | 29.5% | 16.4% | 30.0% | 15.0% |
| **Placebo** | 17.7% | 8.4% | 17.7% | 10.3% |
| **Odds ratio Varenicline vs placebo** | 3.91 p<0.0001 | 3.13 p<0.0001 | 3.85 p<0.0001 | 2.66 p<0.0001 |

**Table 2. Continuous Abstinence during Weeks 9-12 and 9-52 in Preauthorization Studies**

| | Study A3051028 (n=1022) | | Study A3051036 (n=1023) | |
|---|---|---|---|---|
| | **CA Wk 9-12** | **CA Wk 9-52** | **CA Wk 9-12** | **CA Wk 9-52** |
| **Odds ratio Varenicline vs bupropion** | 1.96 p<0.0001 | 1.45 p=0.0640 | 1.89 p<0.0001 | 1.72 p=0.0062 |

CA = Continuous Abstinence, Wk = Week

Across both studies during active treatment, Patient Reported Outcomes measures demonstrated that craving and withdrawal were significantly reduced in patients randomized to varenicline in comparison with placebo. Varenicline also significantly reduced reinforcing effects of smoking that can perpetuate smoking behavior in patients who smoke during treatment compared with placebo.

The definition of CA during weeks 9-12 as primary endpoint and the inclusion of smoking cessation counselling at each clinic visit have been fairly consistent across Phase 3-4 studies.

### Maintenance of Abstinence[37]

A maintenance of abstinence study (A3051035) assessed the benefit of an additional 12 weeks of varenicline therapy on the maintenance of abstinence. Patients in this study (n=1,927) received open-label varenicline 1 mg twice daily for 12 weeks. Patients who stopped smoking by Week 12 were then randomized to receive either varenicline (1 mg twice daily) or placebo for an additional 12 weeks for a total study duration of 52 weeks. This study showed the benefit of an additional 12-week treatment with varenicline 1 mg twice daily for the maintenance of smoking cessation compared to placebo. The odds of maintaining abstinence at week 24, following an additional 12 weeks of treatment with varenicline, were 2.47 times those for placebo (p<0.0001). Superiority to placebo for CA was maintained through week 52 (Odds Ratio [OR]=1.35, p=0.0126).

### Flexible Quit Date[38]

The effect of varenicline 1 mg BID in a flexible, patient-selected quit date setting was assessed in a double-blind, placebo-controlled study of 651 subjects (study A3051095). Subjects were randomized 3:1 to varenicline or placebo for a treatment of 12 weeks and a followed-up post-treatment for another 12 weeks. In this study, 486 subjects received varenicline and 165 received placebo. Patients were instructed to select a quit date after the initial week of dose titration and before the clinical visit at the end of week 5 of treatment. Patients treated with varenicline had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (53.94%) compared to patients treated with placebo (19.4%) (OR 6.03; 95% CI 3.80, 9.56; p<0.0001) and from week 9 through 24 (35.2%) compared to subjects treated with placebo (12.73%) (OR 4.45; 95% CI 2.62, 7.55; p<0.0001).

### Study in Subjects Re-treated with Varenicline[39]

Varenicline was evaluated in a double-blind, placebo-controlled trial of 494 patients who had made a previous attempt to quit smoking with varenicline, and either did not succeed in quitting or relapsed after treatment. Subjects were randomized 1:1 to varenicline 1 mg twice daily (N=249) or placebo (N=245) for 12 weeks of treatment and followed for up to 40 weeks post-treatment. Patients included in this study had taken varenicline for a smoking-cessation attempt in the past (for a total treatment duration of a minimum of two weeks), at least three months prior to study entry, and had been smoking for at least four weeks. Patients treated with varenicline had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (45.0%) compared to patients treated with placebo (11.8%) (OR 7.08; 95% CI 4.34, 11.55; p<0.0001) and from weeks 9 through 52 (20.1%) compared to subjects treated with placebo (3.3%) (OR 9.00; 95% CI 3.97, 20.41; p<0.0001) (Table 3). Adverse events in this study were quantitatively and qualitatively similar to those observed in premarketing studies.

**Table 3. Continuous Abstinence during Weeks 9-12 and 9-52 in Patients Re-treated with Varenicline**

| Week | Varenicline n=249 | Placebo n=245 | Odds ratio (95% CI), p value |
|---|---|---|---|
| CA Wk 9-12 | 45.0% | 11.8% | 7.08 (4.34, 11.55) p<0.0001 |
| CA Wk 9-52 | 20.1% | 3.3% | 9.00 (3.97, 20.41) p<0.0001 |

CA = Continuous Abstinence, CI = Confidence interval, Wk = Week

### Gradual Approach to Quitting Smoking[40]

Varenicline was evaluated in a 52-week double-blind placebo-controlled study of 1,510 subjects who were not able or willing to quit smoking within four weeks but were willing to gradually reduce their smoking over a 12-week period before quitting. Subjects were randomized to either varenicline 1 mg twice daily (n=760) or placebo (n=750) for 24 weeks and followed up post-treatment through week 52. Subjects were instructed to reduce the number of cigarettes smoked by at least 50 percent by the end of the first four weeks of treatment, followed by a further 50 percent reduction from week four to week eight of treatment, with the goal of reaching complete abstinence by 12 weeks. After the initial 12-week reduction phase, subjects continued treatment for another 12 weeks. Subjects treated with varenicline had a significantly higher Continuous Abstinence Rate compared with placebo at weeks 15 through 24 (32.1% vs 6.9%; OR 8.74; 95% CI 6.09, 12.53; p<0.0001) and weeks 21 through 52 (27.0% vs 9.9%; OR 4.02; 95% CI 2.94, 5.50; p<0.0001) (Table 4). The varenicline safety profile in this study was consistent with the premarketing studies.

**Table 4. Continuous Abstinence during Weeks 15-24 and 21-52 in Patients Treated with Varenicline in a Reduce-to-Quit Approach**

| Week | Varenicline n=760 | Placebo n=750 | Odds ratio (95% CI), p value |
|---|---|---|---|
| CA wk 15-24 | 32.1% | 6.9% | 8.74 (6.09, 12.53) p<0.0001 |
| CA wk 21-52 | 27.0% | 9.9% | 4.02 (2.94, 5.50) p<0.0001 |

CA = Continuous Abstinence, CI = Confidence interval, Wk = Week

### Smokers with Cardiovascular Disease[41]

Varenicline was evaluated in a randomized, double-blind, placebo-controlled study of 703 subjects with stable, documented cardiovascular disease (other than or in addition to hypertension) that had been diagnosed for more than 2 months (Study A3051049). Subjects aged 35 to 75 years were randomized to varenicline 1 mg BID or placebo for a treatment period of 12 weeks and then were followed for 40 weeks post-treatment. Subjects treated with varenicline had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (47.3%) compared to subjects treated with placebo (14.3%) (OR 6.05; 95% CI 4.13, 8.86; p<0.0001) and from week 9 through 52 (19.8%) compared to subjects treated with placebo (7.4%) (OR 3.19; 95% CI 1.97, 5.18; p<0.0001) as shown in Table 5.

**Table 5. Continuous Abstinence during Weeks 9-12 and 9-52 in Patients with Stable Cardiovascular Disease**

| Week | Varenicline n=353 | Placebo n=350 | Odds ratio (95% CI), p value |
|---|---|---|---|
| CA Wk 9-12 | 47.3% | 14.3% | 6.05 (4.13, 8.86) p<0.0001 |
| CA Wk 9-52 | 19.8% | 7.4% | 3.19 (1.97, 5.18) p<0.0001 |

CA = Continuous Abstinence, CI = Confidence interval, Wk = Week

### Smokers with Chronic Obstructive Pulmonary Disease[42]

Varenicline was evaluated in a randomized, double-blind, placebo-controlled study of 499 subjects with mild-to-moderate COPD with post-bronchodilator FEV1/FVC <70% and FEV1 ≥50% of predicted normal value. Subjects aged ≥35 years were randomized to varenicline 1 mg BID or placebo for a treatment period of 12 weeks and then were followed for 40 weeks post-treatment. Subjects treated with varenicline had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (42.3%) compared to subjects treated with placebo (8.8%) (OR 8.40; 95% CI 4.99, 14.14; p<0.0001) and from week 9 through 52 (18.6%) compared to subjects treated with placebo (5.6%) (OR 4.04; 95% CI 2.13, 7.67; p<0.0001) as presented in Table 6.

**Table 6. Continuous Abstinence during Weeks 9-12 and 9-52 in Patients with Chronic Obstructive Pulmonary Disease**

| Week | Varenicline n=248 | Placebo n=251 | Odds ratio (95% CI), p value |
|---|---|---|---|
| **CA Wk 9-12** | 42.3% | 8.8% | 8.40 (4.99, 14.14) p<0.0001 |
| **CA Wk 9-52** | 18.6% | 5.6% | 4.04 (2.13, 7.67) p<0.0001 |

CA = Continuous Abstinence, CI = Confidence interval, Wk = Week

### Study in Subjects with Major Depressive Disorder[43]

Varenicline was evaluated in a randomized, double-blind, placebo-controlled study of 525 subjects with major depressive disorder without psychotic features (DSM-IV TR), on stable antidepressant treatment and/or who experienced a major depressive episode in the past 2 years and were successfully treated. Subjects aged 18 to 75 years were randomized to varenicline 1 mg BID or placebo for a treatment period of 12 weeks and then followed for 40 weeks post-treatment. Subjects treated with varenicline had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (35.9%) compared to subjects treated with placebo (15.6%) (OR 3.35; 95% CI 2.16, 5.21; p<0.0001) and from week 9 through 52 (20.3%) compared to subjects treated with placebo (10.4%) (OR 2.36; 95% CI 1.40, 3.98; p=0.0011) (Table 7).

**Table 7. Continuous Abstinence During Weeks 9-12 and 9-52 in Patients with Major Depressive Disorder**

| Week | Varenicline n=256 | Placebo n=269 | Odds ratio (95% CI), p value |
|---|---|---|---|
| CA wk 9-12 | 35.9% | 15.6% | 3.35 (2.16, 5.21) p<0.0001 |
| CA wk 9-52 | 20.3% | 10.4% | 2.36 (1.40, 3.98) p=0.0011 |

CA = Continuous Abstinence, CI = Confidence interval, Wk = Week

### Study in Subjects with and without a History of Psychiatric Disorders[18]

Varenicline was evaluated in a 24-week, double-blind, NRT and placebo-controlled, multicenter, parallel group study designed to assess the safety and efficacy of varenicline 1 mg twice daily (BID) and bupropion hydrochloride 150 mg BID for smoking cessation, with a primary safety focus on estimating the occurrence of neuropsychiatric AEs and main efficacy objectives of measuring continuous abstinence for Weeks 9 to 12 and 9 to 24 in subjects with and without a psychiatric diagnosis. The primary comparisons were varenicline versus placebo and bupropion versus placebo. NRT was included as an active control, and study drugs were given via a triple dummy design, i.e., all patients took 3 drugs, which were either 1 active

plus 2 placebo or all 3 were placebo. This allowed active versus active treatment comparisons, as well as standard active versus placebo comparisons. The duration of active treatment was 12 weeks, followed by a nontreatment follow-up phase for an additional 12 weeks.

In both cohorts and overall, all active treatments showed significantly greater efficacy in smoking cessation compared with placebo as measured at both Weeks 9-12 (Table 8) and 9-24 (Table 9). In addition, varenicline showed significantly greater efficacy compared with bupropion and compared with NRT at both Weeks 9-12 and 9-24, while the bupropion−NRT differences were not significant in either timeframe (Table 8, Table 9).

**Table 8. Treatment Comparison of Continuous Abstinence, Weeks 9-12, CO -Confirmed, by Cohort and Overall**

| | **Overall** | **Non-Psychiatric History** | **Psychiatric History** |
|---|---|---|---|
| **CAR 9-12 (%)** | | n/N (%) | |
| Varenicline | 683/2037 (33.5%) | 382/1005 (38.0%) | 301/1032 (29.2%) |
| Bupropion | 460/2034 (22.6%) | 261/1001 (26.1%) | 199/1033 (19.3%) |
| NRT | 476/2038 (23.4%) | 267/1013 (26.4%) | 209/1025 (20.4%) |
| Placebo | 255/2035 (12.5%) | 138/1009 (13.7%) | 117/1026 (11.4%) |
| **Treatment Comparisons** | **Estimated odds ratio in CAR 9-12 (95% CI)** | | |
| *Primary Comparisons* | | | |
| Varenicline vs Placebo | 3.61 (3.07, 4.24) | 4.00 (3.20, 5.00) | 3.24 (2.56, 4.11) |
| Bupropion vs Placebo | 2.07 (1.75, 2.45) | 2.26 (1.80, 2.85) | 1.87 (1.46, 2.39) |
| *Secondary Comparisons* | | | |
| NRT vs Placebo | 2.15 (1.82, 2.54) | 2.30 (1.83, 2.90) | 2.00 (1.56, 2.55) |
| Varenicline vs Bupropion | 1.75 (1.52, 2.01) | 1.77 (1.46, 2.14) | 1.74 (1.41, 2.14) |
| Varenicline vs NRT | 1.68 (1.46, 1.93) | 1.74 (1.43, 2.10) | 1.62 (1.32, 1.99) |
| Bupropion vs NRT | 0.96 (0.83, 1.11) | 0.98 (0.80, 1.20) | 0.94 (0.75, 1.16) |

CAR = Continuous Abstinence Rate, CI = Confidence interval, CO = Carbon Monoxide, NRT = Nicotine Replacement Therapy

**Table 9. Treatment Comparison of Continuous Abstinence, Weeks 9-24, CO -Confirmed, by Cohort and Overall**

| | Overall | Non-Psychiatric History | Psychiatric History |
|---|---|---|---|
| **CAR 9-24 (%)** | n/N (%) | | |
| Varenicline | 445/2037 (21.8%) | 256/1005 (25.5%) | 189/1032 (18.3%) |
| Bupropion | 330/2034 (16.2%) | 188/1001 (18.8%) | 142/1033 (13.7%) |
| NRT | 320/2038 (15.7%) | 187/1013 (18.5%) | 133/1025 (13.0%) |
| Placebo | 191/2035 (9.4%) | 106/1009 (10.5%) | 85/1026 (8.3%) |
| **Treatment Comparison** | **Estimated odds ratio in CA 9-24 (95% CI)** | | |
| *Primary Comparison* | | | |
| Varenicline vs Placebo | 2.74 (2.28, 3.30) | 2.99 (2.33, 3.83) | 2.50 (1.90, 3.29) |
| Bupropion vs Placebo | 1.89 (1.56, 2.29) | 2.00 (1.54, 2.59) | 1.77 (1.33, 2.36) |
| *Secondary Comparison* | | | |
| NRT vs Placebo | 1.81 (1.49, 2.19) | 1.96 (1.51, 2.54) | 1.65 (1.24, 2.20) |
| Varenicline vs Bupropion | 1.45 (1.24, 1.70) | 1.49 (1.20, 1.85) | 1.41 (1.11, 1.79) |
| Varenicline vs NRT | 1.52 (1.29, 1.78) | 1.52 (1.23, 1.89) | 1.51 (1.19, 1.93) |
| Bupropion vs NRT | 1.04 (0.88, 1.24) | 1.02 (0.81, 1.28) | 1.07 (0.83, 1.39) |

CA = Continuous Abstinence, CAR = Continuous Abstinence Rate, CI = Confidence interval, CO = Carbon Monoxide, NRT = Nicotine Replacement Therapy

### Study in Healthy Adolescent Smokers[44]

Varenicline was evaluated in a 12-week, randomized, double-blind, placebo controlled, parallel group, dose ranging study with 40 weeks of follow-up in healthy adolescent smokers.

This study enrolled 312 nicotine dependent adolescent smokers 12-19 years old, 234 of whom were 12-17 years old. Subjects were randomized 1:1:1 to either high-dose varenicline (1 mg BID or 0.5 mg BID for those < 55 kg), low-dose varenicline (0.5 mg BID or 0.5 mg once daily for those < 55 kg), or placebo. The study included a 12-week treatment period and a 40-week non-treatment follow-up period. All subjects received < 10 minutes of age-appropriate cessation counselling at every study visit, whether in the clinic or by telephone.

The study did not meet the primary endpoint of the urine-cotinine-confirmed CAR from Week 9 to Week 12 in the overall study population of adolescent smokers 12-19 years old for either dose of varenicline compared to placebo. Analyses of

secondary endpoints were consistent with the primary endpoint analysis. Efficacy results analyzed post hoc for the subset of subjects 12-17 years old were similar to those for the overall population. Varenicline was well-tolerated in this study population, with an AE profile similar to that observed in healthy adult smokers and no notable findings for neuropsychiatric AEs.

## 10. Review of harms and toxicity: summary of evidence on safety.

### Introduction

The clinical safety profile of varenicline has been well characterized in more than 20 Pfizer-sponsored, randomized, controlled trials in which varenicline was compared to placebo and active comparators. This cumulative evidence base includes a wide variety of subject populations as detailed further below and includes a large, randomized, active and placebo-controlled trial that provided a comprehensive analysis with regard to the product's overall safety profile.

The data from these randomized, controlled trials, as well as post-marketing safety surveillance and observational studies, demonstrate that varenicline is well tolerated. Nausea and abnormal dreams/insomnia have been identified as AEs consistently related to varenicline. The safety profile of varenicline continues to support a favorable benefit/risk profile for varenicline.

This section provides an overview of the safety data from these clinical trials. In addition, overviews of 2 safety topics of interest that arose from post-marketing case reports are presented: neuropsychiatric events (including suicidal ideation and behavior) and CV events.

### Safety in Randomized Controlled Studies

Eight Phase 2-3 studies, which were conducted in smokers who were otherwise generally healthy, supported the initial authorization of varenicline. The studies included a total of 5944 subjects, 3940 subjects were exposed to varenicline. In most of these studies the treatment period was 12-weeks while in one study it was 24-weeks and in another it was 52-weeks. Most of the studies included nontreatment follow-up to 1 year from start of treatment. These studies demonstrated the acceptable safety and tolerability profile of varenicline in subjects attempting to quit smoking.

In the two Phase 3 pivotal studies (A3051028 and A3051036), which included 692 subjects treated with varenicline, 669 subjects treated with bupropion, and 684 subjects treated with placebo, the most common AEs in the varenicline treatment group were nausea (28.8% varenicline, 9.9% bupropion, 9.1% placebo), headache (14.2% varenicline, 11.1% bupropion, 12.4% placebo), insomnia (14.2% varenicline, 21.5% bupropion, 12.6% placebo), and abnormal dreams (11.7% varenicline, 5.7% bupropion, 4.5% placebo). In the majority of cases, nausea occurred early in the treatment period, was mild to moderate in severity, and did not result in discontinuation of treatment. The incidence of nausea decreased with time on varenicline.[45]

Varenicline has also been studied in several post-authorization studies including (1) a study conducted in smokers with COPD,[42] (2) a study conducted in generally healthy smokers (similar to those in the premarketing studies) in which they were allowed to select a quit date between days 8 and 35 of treatment ("flexible quit date"),[38] (3) a study conducted in smokers who had previously taken varenicline for 2 or more weeks and were not able to quit smoking or who relapsed after quitting smoking ("re-treatment"),[39] (4) a study conducted in patients with stable CVD,[41] (5) a study conducted in patients with stable schizophrenia or schizoaffective disorder,[46] (6) a study conducted in patients with major depressive disorder,[43] (7) a post-approval safety outcome study in patients without or with a history of psychiatric disorder (EAGLES) specifically designed to assess the frequency of neuropsychiatric AEs,[18] and (8) a study in patients who were not able or willing to quit abruptly and who were instructed to quit gradually ("gradual approach to quitting smoking").[40] In addition, post-authorization trials were conducted in specific countries or geographic regions, including in Asia (Japan[47], Taiwan and Korea[48], multi-Asian[49]) as well as a multinational study in the Middle East, Africa, and South America.[50]

The safety profile of varenicline was generally consistent across pre-and post-authorization studies. Data are provided below for a cohort of 6 pre-approval Phase 2-3 studies (2005 Pooled Studies), a cohort of 15 pre-and post-authorization Phase 2-4 studies (2010 Pooled Studies), along with data from the EAGLES study.

**Exposure**

Table 10 shows exposure data in the pooled cohorts. In the 15-study pool, exposure to varenicline was 360,743 subject-days.

**Table 10. Treatment Duration and Exposure for All Treated Subjects in Pooled Study Cohorts**

| | 2005 Pooled Studies | | 2010 Pooled Studies | |
|---|---|---|---|---|
| **Total Number of Subjects** | **Var N=1983** | **Pbo N=1209** | **Var N=4483** | **Pbo N=2892** |
| **Median Days (Range)** | 83.0<br>1-413 | 83.0<br>1-379 | 84.0<br>1-413 | 84.0<br>1-379 |
| **Subject-Days Exposure**[a] | 166,838 | 92,791 | 360,743 | 222,023 |

a. Drug exposure is based on the actual days when subjects received treatment.
Var=varenicline; Pbo=placebo
Protocols included: 2005 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036, A3051037
2010 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036, A3051037, A3051045, A3051046_48, A3051049, A3051054, A3051055, A3051080, A3051095, A3051104, A3051115
Source: FDA Review 2011[51]

Table 11 shows the exposure in the EAGLES study.

**Table 11. Exposure to Treatment, EAGLES Study, Safety Population**

| Statistics (Days) | Varenicline N = 990 | Bupropion N = 989 | NRT N = 1006 | Placebo N = 999 |
|---|---|---|---|---|
| **Non-Psychiatric History** | | | | |
| Mean | 75.92 | 74.61 | 74.53 | 76.13 |
| Q1 - Q3 | 83 - 86 | 81 - 86 | 80 - 86 | 82 - 86 |
| Median | 85 | 85 | 85 | 85 |
| Standard deviation | 21.59 | 22.87 | 22.82 | 21.44 |
| Range | 2 - 103 | 1 - 96 | 1 - 100 | 1 - 110 |
| **Psychiatric History** | | | | |
| Mean | 72.95 | 72.76 | 72.93 | 71.05 |
| Q1 - Q3 | 77 - 86 | 78 - 86 | 78 - 86 | 68 - 85 |
| Median | 85 | 85 | 85 | 85 |
| Standard deviation | 24.46 | 24.69 | 24.33 | 25.37 |
| Range | 1 - 107 | 1 - 98 | 1 - 98 | 1 - 103 |

Abbreviations: N = number of subjects randomized to study treatment who received at least 1 partial dose of study medication; NRT = nicotine replacement therapy.
Q1 and Q3 are the first quartile and third quartile statistics, respectively.
Lost-to-follow-up subjects were imputed as having used all study drug dispensed at last contact visit in a per protocol manner.
Source: FDA Briefing Document 2016[52]

## Adverse Events

Table 12 shows the common AEs in the cohort of pre-authorization studies and the cohort including pre-and post-authorization studies. Table 13 shows common AEs for the EAGLES study overall. Across all studies the most common AEs in varenicline treated subjects and those reported in a greater percentage of varenicline than placebo subjects were: nausea, headache, abnormal dreams, and insomnia.

**Table 12. Commonly Reported Adverse Events (PTs ≥5% in any Treatment Group, Treatment-Related) by SOC in Pooled Study Cohorts**

| | 2005 Pooled Studies | | 2010 Pooled Studies | |
|---|---|---|---|---|
| **Total Number of Subjects** | **Var N=1983** | **Pbo N=1209** | **Var N=4483** | **Pbo N=2892** |
| **SOC** PT | **number (%) of subjects** | | | |
| **Gastrointestinal Disorders** | | | | |
| Constipation | 118 (6.0) | 27 (2.2) | 235 (5.2) | 68 (2.4) |
| Flatulence | 130 (6.6) | 34 (2.8) | 196 (4.4) | 69 (2.4) |
| Nausea | 572 (28.8) | 104 (8.6) | 1221 (27.2) | 241 (8.3) |
| Vomiting | 59 (3.0) | 8 (0.7) | 146 (3.3) | 25 (0.9) |

**Table 12. Commonly Reported Adverse Events (PTs ≥5% in any Treatment Group, Treatment-Related) by SOC in Pooled Study Cohorts**

| | 2005 Pooled Studies | | 2010 Pooled Studies | |
|---|---|---|---|---|
| **Total Number of Subjects** | **Var N=1983** | **Pbo N=1209** | **Var N=4483** | **Pbo N=2892** |
| **SOC** PT | **number (%) of subjects** | | | |
| **General Disorders and Administration Site Conditions** | | | | |
| Fatigue | 86 (4.3) | 40 (3.3) | 176 (3.9) | 77 (2.7) |
| **Nervous System Disorders** | | | | |
| Headache | 217 (10.9) | 116 (9.6) | 444 (9.9) | 227 (7.8) |
| Dizziness | 101 (5.1) | 56 (4.6) | 182 (4.1) | 127 (4.4) |
| Dysgeusia | 155 (7.8) | 45 (3.7) | 194 (4.3) | 72 (2.5) |
| **Psychiatric Disorders** | | | | |
| Abnormal dreams | 240 (12.1) | 56 (4.6) | 395 (8.8) | 84 (2.9) |
| Insomnia | 248 (14.3) | 117 (9.7) | 480 (10.7) | 184 (6.4) |

Var=varenicline; Pbo=placebo.
Includes AEs up to 30 days after the last dose of study drug.
Protocols included: 2005 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036, A3051037
2010 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036, A3051037, A3051045, A3051046_48, A3051049, A3051054, A3051055, A3051080, A3051095, A3051104, A3051115
Source: FDA Review 2011[51]

**Table 13. Most Frequently Reported Treatment-Emergent Adverse Events (≥5% of Subjects in any Treatment Arm), EAGLES Study Overall Safety Population**

| System Organ Class Preferred Term | Study Overall | | | |
|---|---|---|---|---|
| | **Varenicline (N=2016)** | **Bupropion (N=2006)** | **NRT (N=2022)** | **Placebo (N=2014)** |
| **Subjects with Adverse Events** | **1503 (74.6)** | **1446 (72.1)** | **1436 (71.0)** | **1345 (66.8)** |
| **Gastrointestinal Disorders** | **786 (39.0)** | **527 (26.3)** | **481 (23.8)** | **414 (20.6)** |
| Nausea | 511 (25. 3) | 201 (10.0) | 199 (9.8) | 137 (6.8) |
| Dry mouth | 66 (3.3) | 146 (7.3) | 59 (2.9) | 64 (3.2) |
| **General Disorders and Administration Site Conditions** | **270 (13.4)** | **241 (12.0)** | **404 (20.0)** | **229 (11.4)** |
| Application site pruritus | 22 (1.1) | 12 (0.6) | 109 (5.4) | 16 (0.8) |
| Fatigue | 124 (6.2) | 57 (2.8) | 75 (3.7) | 83 (4.1) |
| **Infections and Infestations** | **533 (26.4)** | **475 (23.7)** | **495 (24.5)** | **506 (25.1)** |
| Nasopharyngitis | 174 (8.6) | 156 (7.8) | 126 (6.2) | 135 (6.7) |
| Upper respiratory tract infection | 109 (5.4) | 104 (5.2) | 97 (4.8) | 115 (5.7) |
| **Nervous System Disorders** | **440 (21.8)** | **440 (21.9)** | **443 (21.9)** | **374 (18.6)** |
| Headache | 245 (12.2) | 186 (9.3) | 233 (11.5) | 199 (9.9) |

**Table 13. Most Frequently Reported Treatment-Emergent Adverse Events (≥5% of Subjects in any Treatment Arm), EAGLES Study Overall Safety Population**

| System Organ Class<br>Preferred Term | Study Overall | | | |
|---|---|---|---|---|
| | Varenicline (N=2016) | Bupropion (N=2006) | NRT (N=2022) | Placebo (N=2014) |
| **Psychiatric Disorders** | **720 (35.7)** | **767 (38.2)** | **722 (35.7)** | **613 (30.4)** |
| Anxiety | 132 (6.5) | 169 (8.4) | 138 (6.8) | 120 (6.0) |
| Irritability | 82 (4.1) | 71 (3.5) | 108 (5.3) | 104 (5.2) |
| Abnormal dreams | 201 (10.0) | 131 (6.5) | 251 (12.4) | 92 (4.6) |
| Insomnia | 189 (9.4) | 245 (12.2) | 196 (9.7) | 139 (6.9) |

N=total number of subjects per treatment arm; NRT=nicotine replacement therapy.
Subjects are only counted once per treatment for each row but may be counted in multiple rows.
Includes all subjects who received at least 1 partial dose of study treatment.
Treatment-emergent=during treatment plus 30 days.
MedDRA v18.0
Source: FDA Advisory Committee Sponsor Briefing Document 2016[53]

*Meta-analyses*

The results of a meta-analysis of placebo-controlled clinical trials reported in the 2016 Cochrane Review of nicotine receptor partial agonists for smoking cessation also shows a consistent safety profile for varenicline.[19] In that meta-analysis, the most frequent AE for varenicline-treated smokers was mild to moderate nausea, at rates between 24% and 29% in the majority of studies. The other frequently reported AEs included insomnia, abnormal dreams, and headache. Meta-analyses of these four AEs for varenicline versus placebo resulted in RRs of 3.27 (95% CI, 3.00, 3.55: 32 studies; 14,963 participants) for nausea; 1.49 (95% CI, 1.35, 1.65: 29 studies; 14,447 participants) for insomnia; 2.12 (95% CI, 1.88, 2.38: 26 studies; 13,682 participants) for abnormal dreams; and 1.17 (95% CI, 1.07, 1.29: 25 studies; 13,835 participants) for headache, with all differences being statistically significant.

## Serious Adverse Events Including Deaths

Table 14 shows serious adverse events (SAEs) in the pooled cohorts. The percentage of subjects experiencing at least one all-causality SAE was low and similar between the varenicline and placebo groups in both pooled cohorts (15-study pool: 3.2% vs 3.1%, respectively). Table 15 shows SAEs in EAGLES. In this study the percentages of subjects with SAEs were similar across all treatment groups (1.9% varenicline, 2.4% bupropion, 2.3% NRT, 2.0% placebo).

**Table 14. Serious Adverse Events (All-Causality) in Pooled Cohorts**

| | 2005 Pooled Studies | | 2010 Pooled Studies | |
|---|---|---|---|---|
| **Serious adverse events[a]** | **Var 1983** | **Pbo 1209** | **Var 4483** | **Pbo 2892** |
| Number (%) of subjects | 47 (2.4) | 19 (1.6) | 144 (3.2) | 90 (3.1) |
| Number of serious adverse events | 69 | 24 | 209 | 129 |

a. Includes fatal and nonfatal SAEs reported after the start of treatment and within 28 days after the last dose of study drug.
Var=varenicline; Pbo=placebo
Protocols included: 2005 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036, A3051037
2010 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036, A3051037, A3051045, A3051046_48, A3051049, A3051054, A3051055, A3051080, A3051095, A3051104, A3051115
Source: FDA Review 2011[51]

**Table 15. Serious Adverse Events (All-Causality) in EAGLES**

| | Number (%) of Subjects | | | |
|---|---|---|---|---|
| | **Varenicline** | **Bupropion** | **NRT** | **Placebo** |
| Overall | | | | |
| Subjects Evaluable for AEs | 2016 | 2006 | 2022 | 2014 |
| Subjects with SAEs | 39 (1.9) | 48 (2.4) | 46 (2.3) | 41 (2.0) |

Source: FDA Advisory Committee Sponsor Briefing Document 2016[53]

Table 16 shows deaths in the 15-study cohort. The crude mortality rate as well as the mortality per subject-years was lower in varenicline subjects than placebo subjects.

**Table 16. Mortality (15-study pooled data)**

| Treatment Group | Patients | Deaths | Crude Mortality | Subject-Days Exposure | Mortality per Subject-Days Exposure |
|---|---|---|---|---|---|
| Varenicline | 4483 | 8 | 0.00178 | 360,743 | $2.21 \times 10^{-5}$ |
| Placebo | 289 | 7 | 0.00242 | 222,023 | $3.15 \times 10^{-5}$ |

Source: FDA Review 2011[51]

In the EAGLES study, a total of 10 subjects were reported to have had fatal AEs: none were varenicline subjects. Four of the deaths occurred during treatment or within 30 days of the last study treatment dose: varenicline 0; bupropion 2; nicotine patch 0; placebo 2. The deaths that occurred >30 days after the last study treatment dose were: varenicline 0; bupropion 1; nicotine patch 3; placebo 2.[18]

**Permanent Discontinuation from Treatment Due to Adverse Events**

The most common AEs leading to permanent discontinuation from treatment are shown in Table 17 for the 2 pooled cohorts. Nausea and insomnia were consistently more frequent AEs leading to discontinuation in the varenicline group than the placebo group and are expected AEs of varenicline. In the largest pool (2010 pool), depressed mood was a more frequent AE leading to discontinuation in the varenicline group and depression was a more frequent AE leading to discontinuation in the placebo group. The data from the pooled studies does not appear to indicate a causal relationship between varenicline, depressed mood, and depression.

**Table 17. Adverse Events Resulting in Permanent Discontinuation of Study Treatment (All Causality, ≥1% in any Treatment Group) by SOC, Pooled Cohorts**

| | 2005 Pooled Studies | | 2010 Pooled Studies | |
|---|---|---|---|---|
| **Total Number Subjects** | **Varenicline N=1983** | **Placebo N=1209** | **Varenicline N=4483** | **Placebo N=2892** |
| **Number (%) Subjects** | n (%) | n (%) | n (%) | n (%) |
| **Gastrointestinal Disorders** | **95 (4.8)** | **20 (1.7)** | **156 (3.5)** | **34 (1.2)** |
| Nausea | 59 (3.0) | 5 (0.4) | 96 (2.1) | 10 (0.3) |
| **Psychiatric disorders** | **75 (3.8)** | **34 (2.8)** | **104 (2.3)** | **58 (2.0)** |
| Depressed mood | 5 (0.3) | 0 (0) | 9 (0.2) | 3 (0.1) |
| Depression | 10 (0.5) | 5 (0.4) | 13 (0.3) | 11 (0.4) |
| Insomnia | 25 (1.3) | 11 (0.9) | 30 (0.7) | 14 (0.5) |

Includes AEs up to 30 days after the last dose of study drug.
Protocols included: 2005 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036 A3051037
2010 pooled studies: A3051002, A3051007, A3051016, A3051028, A3051036 A3051037, A3051045, A3051046_48, A3051049, A3051054, A3051055, A3051080, A3051095, A3051104, A3051115
Source: FDA Review 2011

In the EAGLES study population overall, the percentage of subjects who discontinued study treatment due to AEs were similar across the 3 active treatments (8.2% varenicline, 8.8% bupropion, 8.0% NRT) and higher than in placebo subjects (6.1%).[53] Table 18 shows the percentages by cohort (non-psychiatric history vs psychiatric history) for both all causality AEs and the neuropsychiatric composite endpoint events. Higher percentages of subjects in the psychiatric cohort discontinued study treatment due to AEs, either all-causality or neuropsychiatric composite endpoint events, than subjects in the nonpsychiatric group. Within the psychiatric cohort the percentages tended to be similar across treatment groups.

**Table 18. Adverse Events Leading to Discontinuation of Study Treatment, EAGLES**

| | Non-Psychiatric History | | | | Psychiatric History | | | |
|---|---|---|---|---|---|---|---|---|
| | Var N=990 | Bup N=989 | NRT N=1006 | Pbo N=999 | Var N=1026 | Bup N=1017 | NRT N=1016 | Pbo N=1015 |
| All-causality AEs | 57 (5.8) | 75 (7.6) | 74 (7.4) | 29 (2.9) | 109 (10.6) | 101 (9.9) | 88 (8.7) | 93 (9.2) |
| Neuropsychiatric composite endpoint events | 1 (0.1%) | 5 (0.5%) | 7 (0.7%) | 3 (0.3%) | 16 (1.6%) | 15 (1.5%) | 12 (1.2%) | 15 (1.5%) |

Var=varenicline; Bup=bupropion; NRT=nicotine replacement therapy; PBO=placebo.
Source: Anthenelli et al 2016[18]

## Safety Topics of Interest

Two safety topics that have been of concern because of a potential association with the use of varenicline, are neuropsychiatric safety and cardiovascular safety.

## Neuropsychiatric Safety

A concern about the neuropsychiatric safety of patients treated with varenicline was initially driven by case reports from post-marketing surveillance that included events such as suicidal ideation and behavior and completed suicide, changes in mood, psychosis, aggression, and hostility. Given that varenicline is used during smoking cessation, which may be associated with neuropsychiatric events in the absence of drug treatment, the relationship between these events and varenicline was not clear.

Pfizer conducted the EAGLES study, a large randomized, double-blind, triple-dummy, active and placebo-controlled study, to evaluate the neuropsychiatric safety and efficacy of varenicline 1 mg BID and bupropion SR 150 mg BID compared with placebo and NRT (patch: 21 mg/day with taper) for smoking cessation in subjects without and with a history of psychiatric disorders.[18] The study, which was requested by, and designed in consultation with, the Food and Drug Administration (FDA) and was also a post-authorization safety study in the European Union, enrolled over 8000 subjects.

In each study treatment arm, subjects were divided into 2 cohorts—those without a psychiatric diagnosis (non-psychiatric cohort) and those with a current or past history of affective, anxiety, psychotic, or personality disorders (psychiatric cohort). The primary endpoint was a composite of moderate and/or severe AEs comprising anxiety, depression, feeling abnormal, hostility, agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, irritability, suicidal ideation, suicidal behavior, and completed suicide.

The results of the primary composite endpoint are shown in Table 19 (observed rates) and Table 20 (model-based analysis). In the overall study population, varenicline was not associated with an increased incidence of clinically significant

neuropsychiatric AEs in the composite primary endpoint. In the non-psychiatric cohort, the incidence of events that comprised the primary endpoint was similar for varenicline and placebo (1.3% and 2.4%, respectively). In the psychiatric cohort, the incidence of events in the composite endpoint was higher for each of the active treatments compared to placebo (varenicline: 6.5%, bupropion: 6.7%, NRT: 5.2% and placebo: 4.9%). However, in the psychiatric cohort, the 95% Confidence Intervals (CIs) for all risk differences for treatment relative to placebo included zero.[18]

**Table 19. Observed Rate for the Primary NPS AE Endpoint, Overall and by Cohort**

| Cohort | Varenicline n/N (%) | Bupropion n/N (%) | NRT n/N (%) | Placebo n/N (%) |
|---|---|---|---|---|
| Overall | 80/2016 (4.0) | 90/2006 (4.5) | 79/2022 (3.9) | 74/2014 (3.7) |
| Non-Psychiatric History | 13/990 (1.3) | 22/989 (2.2) | 25/1006 (2.5) | 24/999 (2.4) |
| Psychiatric History | 67/1026 (6.5) | 68/1017 (6.7) | 54/1016 (5.3) | 50/1015 (4.9) |

N=number of subjects per treatment arm; n=number of subjects with an NPS endpoint AE; NPS AE=neuropsychiatric adverse event; NRT=nicotine replacement therapy.
Includes treatment emergent all causality events
Includes all subjects who received at least 1 partial dose of study treatment.
Source: FDA Advisory Committee Briefing Document 2016[53]

**Table 20. Estimation of the Primary NPS AE Endpoint, Overall and by Cohort and Risk Differences for All Treatment Comparisons**

| | Overall (N=8058) | Non-Psychiatric History (N=3984) | Psychiatric History (N=4074) |
|---|---|---|---|
| **Treatment Arm** | **Estimated[a] NPS AE (% [95% CI])** | | |
| Varenicline | 3.83 (3.02, 4.65) | 1.25 (0.60, 1.90) | 6.42 (4.91, 7.93) |
| Bupropion | 4.53 (3.63, 5.42) | 2.44 (1.52, 3.36) | 6.62 (5.09, 8.15) |
| NRT | 3.80 (2.97, 4.63) | 2.31 (1.37, 3.25) | 5.29 (3.92, 6.66) |
| Placebo | 3.68 (2.87, 4.49) | 2.53 (1.59, 3.47) | 4.83 (3.51, 6.15) |
| **Treatment Comparisons** | **Risk Difference[b] in NPS AE (% [95% CI])** | | |
| **Primary Comparisons** | | | |
| Varenicline vs Placebo | 0.16 (-0.99, 1.30) | -1.28 (-2.40, -0.15) | 1.59 (-0.42, 3.59) |
| Bupropion vs Placebo | 0.85 (-0.35, 2.05) | -0.08 (-1.37, 1.21) | 1.78 (-0.24, 3.81) |
| **Secondary Comparisons** | | | |
| NRT vs Placebo | 0.12 (-1.04, 1.28) | -0.21 (-1.55, 1.12) | 0.46 (-1.45, 2.36) |
| Varenicline vs Bupropion | -0.70 (-1.90, 0.51) | -1.19 (-2.30, -0.09) | -0.20 (-2.34, 1.95) |

**Table 20. Estimation of the Primary NPS AE Endpoint, Overall and by Cohort and Risk Differences for All Treatment Comparisons**

| | Overall (N=8058) | Non-Psychiatric History (N=3984) | Psychiatric History (N=4074) |
|---|---|---|---|
| Varenicline vs NRT | 0.03 (-1.13, 1.20) | -1.06 (-2.21, 0.08) | 1.13 (-0.91, 3.17) |
| Bupropion vs NRT | 0.73, (-0.49, 1.95) | 0.13 (-1.19, 1.45) | 1.33 (-0.73, 3.38) |

a. Based on least-squares means analysis, point estimate, and its 95% CI.
b. Risk difference was based on a generalized linear model with terms for treatment, cohort, region, and treatment by cohort interaction. Region used 2-level classification (United States, non-United States).
CI=confidence interval; N=number of subjects per treatment arm; NPS AE=neuropsychiatric adverse event; NRT=nicotine replacement therapy.
Includes all subjects who received at least 1 partial dose of study treatment.
Source: FDA Advisory Committee Briefing Document 2016[53]

There was one completed suicide reported in the study, which occurred during treatment in a patient treated with placebo in the non-psychiatric cohort. There were no completed suicides reported in the psychiatric cohort. The frequency of suicidal ideation during the treatment period as well as during post-treatment follow-up was similar across treatment groups including placebo. Based on the Columbia-Suicide Severity Rating Scale, in the non-psychiatric history cohort ≤1% of subjects across treatment groups reported suicidal ideation and/or behavior during treatment and ≤30 days after treatment, while in the psychiatric cohort the percentages for the same time period were 3% varenicline, 1% bupropion, 2% NRT and 2% placebo.[18]

*Meta-analyses*

Several meta-analyses of neuropsychiatric AEs in clinical studies with varenicline have shown similar results to the EAGLES study. A large meta-analysis conducted prior to the completion of the EAGLES trial included 39 placebo-controlled trials with a total of 10,761 participants. The analysis found no increased risk for suicide or suicide attempt, suicidal ideation, depression, irritability, or aggression, and reported a reduced risk of anxiety in varenicline compared to placebo (ORs ranging from 0.58 to 1.67, 95% CIs included 1). There was an increased risk of some sleep-related events with varenicline, including insomnia and abnormal dreams, as well as fatigue (ORs ranging from 1.28 to 2.38, 95% CIs >1).[54]

The 2016 Cochrane database systematic review of nicotine receptor partial agonists for smoking cessation that included the EAGLES trial, included a meta-analysis of neuropsychiatric serious AEs. The RR for depression was 0.94 (95% CI, 0.77, 1.14; 36 studies; 16,189 participants), and the RR for suicidal ideation was 0.68 (95% CI, 0.43, 1.07; 24 studies; 11,193 participants), both with non-significantly lower rates in the varenicline groups compared to placebo.[19]

In totality, available data shows no evidence of an increased risk of clinically significant neuropsychiatric events with varenicline.

### Cardiovascular Safety

The risk for cardiovascular (CV) events in patients taking varenicline has been studied in individual clinical trials as well as several meta-analyses. In one Pfizer trial of patients with stable CVD[41], the overall CV event rate was low and all-cause and CV mortality was lower in patients treated with varenicline than with placebo. However, certain nonfatal events occurred more frequently in patients treated with varenicline (incidence of nonfatal myocardial infarction: 1.1% vs. 0.3%, respectively).

Another study in CV patients has been reported in the literature.[55] In this study, 302 patients with acute coronary syndrome (ACS) were randomized to varenicline or placebo. Major Adverse Cardiovascular Events (MACE) were collected during the study period and for 30 days post treatment discontinuation. MACE were reported for 4.0% of patients in the varenicline group and 4.6% of patients in the placebo group.

CV events were also prospectively collected and adjudicated during the EAGLES study and as part of 28-week non-treatment follow-up to EAGLES. This extension allowed for a total of 52 weeks of CV safety data collection. This study provides further evidence that varenicline is not associated with an increased risk of CV AEs in smokers treated for up to 12 weeks and followed for up to 1 year compared to placebo, although because of the relatively low number of events overall, the upper bounds of the 95% CIs for HRs and risk differences do not entirely preclude an association.[56]

*Meta-analyses*

Meta-analyses of CV events in varenicline clinical trials have produced inconsistent findings, with some analyses suggesting an increased in CV events in varenicline-treated subjects,[57,58,] and others suggesting no effect of treatment with varenicline.[59,60,61] Methodological differences, the size and duration of the studies, as well as the low number of CV events overall, likely contribute to the different results.

## 11. Summary of available data on comparative cost and cost effectiveness

### Overview of the various pharmacoeconomic models used in smoking cessation intervention

Varenicline has been evaluated using several economic models such as the DES model and the BENESCO model. The latter (BENESCO) has been used to support the evaluation of varenicline by multiple HTA bodies and will be the focus of the cost effectiveness discussion in this section.[20] It is important to consider that none of these analyses have modeled the impact of multi-source generic varenicline, which would be expected to significantly alter the cost effectiveness evaluation of any medicine. Based on the timing and review of the present submission, should

varenicline be adopted to the EML, it is a possibility that multiple generic sources of varenicline will be in market. Thus, the information below should be evaluated in that context with the understanding that assumptions around cost are likely to change in the near future.

### Summary of available comparative cost-effectiveness data

Overall, smoking cessation therapy is believed to be a cost-effective intervention.[2] The BENESCO model, which was adapted from the Health Economic Consequences of Smoking model originally developed by the WHO European Partnership Project, has been applied to various countries in Europe, South America, Asia and the United States.[20,62] In general, these analyses were conducted from a healthcare payer perspective and simulated a single quit attempt over a one year period and assessed the impact (ie, cost associated with smoking cessation treatment and the development of smoking-attributable morbidity and mortality) over a time horizon of 2, 5, 10, 20, 50 years and/or a lifetime.[20,21,22] In several published evaluations, 12 weeks of therapy with varenicline was predicted to be more effective and less costly from the healthcare payer perspective over a 20 year or lifetime horizon, relative to bupropion, NRT, or unaided quitting in: the United States, Belgium, Netherlands, Germany, Spain, Sweden, Scotland, United Kingdom, Mexico, Czech Republic, Finland, Hong Kong, and Colombia.[20,21,22] These results are relatively consistent across countries with different levels of economic development, however most of the assessments have taken place in high and middle-income countries. HTA bodies in several markets have concluded that treatment with varenicline has an acceptable cost-benefit profile as evidenced by its reimbursement status in countries across several regions including North America, Europe, Africa, the Middle East and Asia Pacific.

## REGULATORY INFORMATION

### 12. Summary of regulatory status of the medicine.

Varenicline tartrate has been granted approval by the US FDA as CHANTIX®, and it has been granted approval by the European Medicines Agency (EMA); Australian Government, Department of Health, Therapeutic Goods Administration; Japanese Pharmaceuticals and Medical Devices Agency, and Health Canada as CHAMPIX®.

A summary listing of the active global regulatory approvals for CHAMPIX® (Varenicline tartrate) and CHANTIX® (Varenicline tartrate) as of November 2020 is provided below.

| Country | Product Detail Set Name | Local Trade Name | Product Approval Date |
|---|---|---|---|
| ARGENTINA | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX 0,5 mg comprimidos recubiertos | CHAMPIX 0,5 mg comprimidos recubiertos | 07-Dec-2006 |
| ARGENTINA | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX 1 mg comprimidos recubiertos | 07-Dec-2006 |

| Country | Product Detail Set Name | Local Trade Name | Product Approval Date |
|---|---|---|---|
| | 1 mg comprimidos recubiertos | | |
| ARGENTINA | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX 0,5 mg y 1 mg comprimidos recubiertos | 01-Aug-2008 |
| ARMENIA | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 21-Jan-2008 |
| ARMENIA | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 21-Jan-2008 |
| AUSTRALIA | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated COMBO PACK CHAMPIX | CHAMPIX | 15-Feb-2007 |
| AUSTRALIA | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 15-Feb-2007 |
| AUSTRIA | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| AUSTRIA | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| BAHRAIN | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 11-Jan-2007 |
| BAHRAIN | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 11-Jan-2007 |
| BAHRAIN | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 18-Sep-2013 |
| BANGLADESH | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX Film Coated Tablets | CHAMPIX Tablets 0.5 mg | 25-Jul-2011 |
| BANGLADESH | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX Film Coated Tablets | CHAMPIX Tablets 1 mg | 25-Jul-2011 |
| BELGIUM | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| BELGIUM | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| BELGIUM | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| BELIZE | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX 0.5 mg Film Coated Tablets | Unknown |
| BELIZE | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX 1 mg Film Coated Tablets | Unknown |
| BOTSWANA | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX 0.5 mg | CHAMPIX 0.5 mg | 25-Apr-2012 |
| BOTSWANA | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX 1 mg | CHAMPIX 1 mg | 25-Apr-2012 |

| Country | Product Detail Set Name | Local Trade Name | Product Approval Date |
|---|---|---|---|
| BRAZIL | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX 0,5 mg Comprimido Revestido | 18-Sep-2006 |
| BRAZIL | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX 0,5 mg + 1 mg Comprimido Revestido | 18-Sep-2006 |
| BRAZIL | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX 1 mg Comprimido Revestido | 18-Sep-2006 |
| BRUNEI DARUSSALAM | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX 1 mg film-coated tablets | 30-Jul-2013 |
| BRUNEI DARUSSALAM | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX 0.5 mg and 1 mg film-coated tablets | 27-Aug-2013 |
| BRUNEI DARUSSALAM | Varenicline tartrate 0.5 mg, Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX 0.5 mg and 1 mg film-coated tablets | 27-Aug-2013 |
| BULGARIA | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| CANADA | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX 0.5 mg Tablet | 24-Jan-2007 |
| CANADA | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX 1 mg Tablet | 24-Jan-2007 |
| CHILE | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 09-Mar-2007 |
| CHILE | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX Comprimidos Recubiertos 1 mg | CHAMPIX Comprimidos Recubiertos 1 mg | 09-Mar-2007 |
| CHINA | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 31-Jul-2008 |
| CHINA | Varenicline tartrate 0.5 mg, Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 31-Jul-2008 |
| CHINA | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 31-Jul-2008 |
| COLOMBIA | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX 0.5 mg | CHAMPIX 0.5 mg Tabletas Recubiertas | 14-Dec-2007 |
| COLOMBIA | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX 1mg | CHAMPIX 1 mg Tabletas Recubiertas | 14-Dec-2007 |
| COSTA RICA | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX 0.5 mg Tabletas Recubiertas | CHAMPIX 0.5 mg Tabletas Recubiertas | 15-Aug-2007 |
| COSTA RICA | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX 1 mg Tabletas Recubiertas | CHAMPIX 1 mg Tabletas Recubiertas | 15-Aug-2007 |
| CROATIA | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |

| Country | Product Detail Set Name | Local Trade Name | Product Approval Date |
|---|---|---|---|
| CROATIA | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| CROATIA | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| CYPRUS | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| CYPRUS | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| CYPRUS | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| CZECH REPUBLIC | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | -- |
| CZECH REPUBLIC | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| CZECH REPUBLIC | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| DENMARK | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| DENMARK | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| DOMINICAN REPUBLIC | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX 0.5 mg Tabletas Recubiertas | 24-Jul-2008 |
| DOMINICAN REPUBLIC | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX 1 mg Tabletas Recubiertas | 22-Aug-2008 |
| EGYPT | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 28-Aug-2008 |
| EGYPT | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 28-Aug-2008 |
| ESTONIA | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| ESTONIA | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| ESTONIA | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| EUROPEAN UNION | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| EUROPEAN UNION | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| EUROPEAN UNION | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| FINLAND | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| FINLAND | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |

| Country | Product Detail Set Name | Local Trade Name | Product Approval Date |
|---|---|---|---|
| FRANCE | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| FRANCE | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| FRANCE | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| GEORGIA | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 15-Mar-2010 |
| GEORGIA | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 15-Mar-2010 |
| GERMANY | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| GERMANY | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| GERMANY | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| GREECE | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| GREECE | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| GREECE | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| GUATEMALA | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX 0.5 mg Tabletas Recubiertas | CHAMPIX 0.5 mg Tabletas Recubiertas | 18-Jul-2007 |
| GUATEMALA | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX 1 mg Tabletas Recubiertas | CHAMPIX 1 mg Tabletas Recubiertas | 18-Jul-2007 |
| HONDURAS | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX 0.5 mg Tabletas Recubiertas | CHAMPIX 0.5 mg Tabletas Recubiertas | 14-Aug-2007 |
| HONDURAS | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX 1 mg Tabletas Recubiertas | CHAMPIX 1 mg Tabletas Recubiertas | 14-Aug-2007 |
| HONG KONG | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX Tab 0.5 mg | 25-Mar-2007 |
| HONG KONG | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX Tab 0.5 mg & 1 mg | 25-Mar-2007 |
| HONG KONG | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX Tab 1 mg | 25-Mar-2007 |
| HUNGARY | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| HUNGARY | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| HUNGARY | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| ICELAND | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |

| Country | Product Detail Set Name | Local Trade Name | Product Approval Date |
|---|---|---|---|
| ICELAND | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| ICELAND | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| INDIA | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX Tablets 0.5 mg | 30-May-2007 |
| INDIA | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX Tablets 1 mg | 30-May-2007 |
| IRAN (ISLAMIC REPUBLIC OF) | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 23-Jan-2016 |
| IRAN (ISLAMIC REPUBLIC OF) | Varenicline tartrate 1 mg Tablet, Film Coated | CHAMPIX | 23-Jan-2016 |
| IRELAND | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| IRELAND | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| IRELAND | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| ISRAEL | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX 0.5 mg | CHAMPIX 0.5 mg | 13-Dec-2007 |
| ISRAEL | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX 1 mg | CHAMPIX 1 mg | 13-Dec-2007 |
| ITALY | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| ITALY | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| ITALY | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| JAPAN | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX Tablets 0.5 mg | 25-Jan-2008 |
| JAPAN | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX Tablets 1 mg | 25-Jan-2008 |
| JORDAN | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 11-Oct-2007 |
| JORDAN | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 16-Oct-2007 |
| JORDAN | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 17-Oct-2007 |
| KOREA (REPUBLIC OF) | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX Tablets 0.5 mg | 30-Mar-2007 |
| KOREA (REPUBLIC OF) | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX Tablets 1 mg | 30-Mar-2007 |
| KUWAIT | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 14-May-2007 |
| KUWAIT | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 14-May-2007 |

| Country | Product Detail Set Name | Local Trade Name | Product Approval Date |
|---|---|---|---|
| KUWAIT | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 11-Sep-2014 |
| KYRGYZSTAN | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 10-Mar-2010 |
| KYRGYZSTAN | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 10-Mar-2010 |
| LATVIA | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| LATVIA | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| LATVIA | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| LEBANON | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX starter pack | CHAMPIX starter pack | 09-Dec-2014 |
| LEBANON | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 09-Dec-2014 |
| LIECHTENSTEIN | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| LIECHTENSTEIN | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| LIECHTENSTEIN | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| LITHUANIA | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| LITHUANIA | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| LITHUANIA | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| LUXEMBOURG | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| LUXEMBOURG | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| MACAO | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX Tab 0.5 mg &1 mg | Unknown |
| MACAO | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX Tab 1 mg | Unknown |
| MALAYSIA | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX 0.5 mg film-coated Tablets | CHAMPIX 0.5 mg and 1 mg film-coated tablets | 31-Jan-2008 |
| MALAYSIA | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX 1.0 mg Film-Coated Tablets | CHAMPIX 1.0 mg Film-Coated Tablets | 31-Jan-2008 |
| MALTA | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |

| Country | Product Detail Set Name | Local Trade Name | Product Approval Date |
|---|---|---|---|
| MALTA | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| MALTA | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| MEXICO | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 28-Sep-2006 |
| MEXICO | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX 0.5 mg Tableta | CHAMPIX 0.5 mg Tableta | 03-Jun-2009 |
| MEXICO | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX 1 mg Tableta | 03-Jun-2009 |
| MOROCCO | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX 0,5 mg et 1 mg | 17-Dec-2007 |
| MOROCCO | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX 1 mg | 17-Dec-2007 |
| NAMIBIA | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX 0.5 mg | CHAMPIX 0.5 mg | 01-Mar-2012 |
| NAMIBIA | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX 1 mg | CHAMPIX 1 mg | 01-Mar-2012 |
| NETHERLANDS | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| NETHERLANDS | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| NETHERLANDS | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| NEW ZEALAND | Varenicline tartrate 0.5 mg Tablet, Film Coated Varenicline Pfizer | Varenicline Pfizer | 28-May-2018 |
| NEW ZEALAND | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated Varenicline Pfizer | Varenicline Pfizer | 28-May-2018 |
| NEW ZEALAND | Varenicline tartrate 1 mg Tablet, Film Coated Varenicline Pfizer | Varenicline Pfizer | 28-May-2018 |
| NORWAY | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| NORWAY | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| NORWAY | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| OMAN | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 01-Jan-2011 |
| OMAN | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 01-Jan-2011 |
| PALESTINE, STATE OF | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX 0.5 mg | 15-May-2017 |

| Country | Product Detail Set Name | Local Trade Name | Product Approval Date |
|---|---|---|---|
| PALESTINE, STATE OF | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX 1 mg | 15-May-2017 |
| PANAMA | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX 1 mg Tabletas Recubiertas | CHAMPIX 1 mg Tabletas Recubiertas | 11-Apr-2008 |
| PANAMA | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX 0.5 mg Tabletas Recubiertas | CHAMPIX 0.5 mg Tabletas Recubiertas | 10-Mar-2009 |
| PHILIPPINES | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 13-Jun-2007 |
| PHILIPPINES | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 13-Jun-2007 |
| POLAND | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| POLAND | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| PORTUGAL | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| PORTUGAL | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| PORTUGAL | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| QATAR | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 09-Jan-2010 |
| QATAR | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 09-Jan-2010 |
| QATAR | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 09-Jun-2010 |
| ROMANIA | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| ROMANIA | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 12-Jan-2018 |
| ROMANIA | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| RUSSIAN FEDERATION | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 11-Aug-2008 |
| RUSSIAN FEDERATION | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 11-Aug-2008 |
| SAUDI ARABIA | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 21-Apr-2008 |
| SAUDI ARABIA | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 21-Apr-2008 |
| SAUDI ARABIA | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Vantix Film Coated | Vantix | 24-Jul-2018 |
| SAUDI ARABIA | Varenicline tartrate 1 mg Tablet, Film Coated Vantix Tabuk | Vantix | 24-Jul-2018 |

| Country | Product Detail Set Name | Local Trade Name | Product Approval Date |
|---|---|---|---|
| SINGAPORE | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX Tablet Starter Pack | CHAMPIX Tablet Starter Pack | 01-Aug-2007 |
| SINGAPORE | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX Tablet 1 mg | CHAMPIX Tablet 1 mg | 01-Aug-2007 |
| SLOVAKIA | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| SLOVAKIA | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| SLOVAKIA | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| SLOVENIA | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| SLOVENIA | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| SLOVENIA | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| SOUTH AFRICA | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX 0.5 mg | CHAMPIX 0.5 mg | 26-Nov-2010 |
| SOUTH AFRICA | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX 1 mg | CHAMPIX 1 mg | 26-Nov-2010 |
| SPAIN | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| SPAIN | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| SPAIN | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| SWEDEN | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| SWEDEN | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| SWEDEN | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| SWITZERLAND | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX 0.5 mg Filmtablette | 21-Dec-2006 |
| SWITZERLAND | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX 0.5 mg und 1 mg Filmtablette | 21-Dec-2006 |
| SWITZERLAND | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX 1 mg Filmtablette | 21-Dec-2006 |
| TAIWAN (PROVINCE OF CHINA) | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX film coated tablet 0.5 mg | CHAMPIX film coated tablet 0.5 mg | 15-Jun-2007 |
| TAIWAN (PROVINCE OF CHINA) | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX film coated tablet 1.0 mg | CHAMPIX film coated tablet 1.0 mg | 15-Jun-2007 |

| Country | Product Detail Set Name | Local Trade Name | Product Approval Date |
|---|---|---|---|
| THAILAND | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX (Tablets 0.5 mg and 1 mg) | 25-Jul-2008 |
| THAILAND | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX (Tablets 1 mg) | CHAMPIX (Tablets 1 mg) | 25-Jul-2008 |
| TURKEY | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 24-Jun-2008 |
| TURKEY | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 24-Jun-2008 |
| UKRAINE | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 19-Feb-2009 |
| UKRAINE | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 23-Oct-2010 |
| UNITED ARAB EMIRATES | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 19-Mar-2007 |
| UNITED ARAB EMIRATES | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 19-Mar-2007 |
| UNITED KINGDOM | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| UNITED KINGDOM | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| UNITED KINGDOM | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 26-Sep-2006 |
| UNITED STATES | Varenicline tartrate 0.5 mg Tablet, Film Coated CHANTIX | CHANTIX | 10-May-2006 |
| UNITED STATES | Varenicline tartrate 1 mg Tablet, Film Coated CHANTIX | CHANTIX | 10-May-2006 |
| URUGUAY | Varenicline tartrate 0.5 mg + Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 21-Dec-2006 |
| URUGUAY | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX 1 mg | 21-Dec-2006 |
| VENEZUELA, BOLIVARIAN REPUBLIC OF | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX 0.5 mg Tabletas Recubiertas | CHAMPIX 0.5 mg Tabletas Recubiertas | 05-Nov-2007 |
| VENEZUELA, BOLIVARIAN REPUBLIC OF | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX 1 mg Tabletas Recubiertas | CHAMPIX 1 mg Tabletas Recubiertas | 05-Nov-2007 |
| VIET NAM | Varenicline tartrate 0.5 mg, Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 23-Dec-2010 |
| VIET NAM | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX | CHAMPIX | 23-Dec-2010 |
| ZIMBABWE | Varenicline tartrate 0.5 mg Tablet, Film Coated CHAMPIX 0.5 mg | CHAMPIX 0.5 mg | 24-Feb-2014 |
| ZIMBABWE | Varenicline tartrate 1 mg Tablet, Film Coated CHAMPIX 1 mg | CHAMPIX 1 mg | 24-Feb-2014 |

## 13. Availability of pharmacopoeia standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia).

Varenicline is not listed on the British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, or European Pharmacopeia.

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